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RESEARCH ARTICLE

Cognitive determinants of decisional capacity in neurodegenerative disorders

Makayla Portley[1], Carolyn Sherer[1], Tianxia Wu[1], Jennifer Farren[2], Laura E. Danielian[1], Sonja W. Scholz[1], Bryan J. Traynor[3], Michael E. Ward[1], Taryn Haselhuhn[1], Allison Snyder[1,*] & Justin Y. Kwan[1,*]

[1]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA
[2]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA
[3]National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA

Correspondence
Allison Snyder and Justin Y. Kwan, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 1D45, MSC 1140, 10 Center Drive, Bethesda, MD 20892, USA.
Tel: +1 301 496 7428; Fax: +1 301 480 0524; E-mail: allison.snyder@nih.gov and justin.kwan@nih.gov

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*These authors contributed equally to this work.

Abstract

Objective: Cognitive contributions to decisional capacity are complex and not well understood. Capacity to consent for research has been linked to executive function, but executive function assessment tools are imperfect. In this study, we examine the relationship between decisional capacity and a newly developed executive function composite score and determine whether cognitive performance can predict impaired decisional capacity. **Methods**: This is a cross sectional study of participants at the National Institutes of Health with frontotemporal dementia-amyotrophic lateral sclerosis spectrum disorders enrolled between 2017 and 2022. A structured interview tool was used to ascertain research decisional capacity. Study participant Uniform Data Set (v3.0) executive function (UDS3-EF) composite score, Clinical Dementia Rating Scale©, and Neuropsychiatric Inventory was determined. **Results**: A decrease in UDS3-EF composite score significantly increased the odds of impaired decisional capacity (OR = 2.92, 95% CI [1.66–5.13], $p = 0.0002$). Executive function was most impaired in frontotemporal dementia (−2.86, SD = 1.26) and least impaired in amyotrophic lateral sclerosis (−0.52, SD = 1.25) participants. The UDS3-EF composite score was also strongly correlated to the Clinical Dementia Rating Scale©. **Interpretation**: Decisional capacity is intrinsically related to executive function in neurodegenerative disorders, and executive dysfunction may predict a lack of decisional capacity alerting investigators of the need for additional scrutiny during the informed consent process.

Introduction

Informed consent is central to the principle of patient autonomy, one of the pillars of medical ethics. In vulnerable populations, such as individuals with neurodegenerative disorders, informed consent takes on even greater importance and requires additional levels of protection and higher scrutiny. Determining a patient's capacity to provide informed consent is vital to both clinical care and research. The key elements of capacity are understanding, communicating a choice, appreciation, and reasoning, any of which may be impaired in this vulnerable population.[1]

The relationship between capacity and cognitive impairment is complex. While a diagnosis of dementia is not synonymous with a lack of capacity,[2] individuals with disorders that cause impaired cognition, such as Alzheimer's disease (AD), are at increased risk for losing decisional capacity.[2,3] Often, the determination of capacity is left to subjective measures by clinicians, the outcomes of which have been shown to be highly variable.[4]

In previous studies, elements of executive function have been closely associated with decisional capacity.[5–7] Executive function is a term given to a group of cognitive processes related to goal-driven behavior consisting of four main subdomains—working memory, inhibition, set shifting, and fluency.[8] Different cognitive tests can be used to quantify impairment in each EF subdomain such

as backward digit span, Stroop test, Trails Making Test B, and letter fluency respectively.[8]

Quantifying EF is difficult to operationalize. Individual tests often target a single EF subdomain.[9] However, assessing global EF with standardized combinations of tests such as the Delis Kaplan Executive Function System (D-KEFS) may lead to an overestimation of EF impairment.[10–12] Furthermore, these neuropsychological batteries are long and especially burdensome for cognitively impaired patients to complete. Additionally, they are vulnerable to non-cognitive factors, such as motor impairment, which can affect participant performance and confound the interpretation of results.

Composite scores have been developed to reduce many of the limitations associated with single tests and standardized psychometric test sets. The benefits of composite scores include increasing statistical power, decreasing bias that arises from missing data, and diminishing the impact of skewed test scores seen in patients with cognitive impairment. Recently the National Alzheimer's Coordinating Center (NACC) Uniform Data Set was used to develop and validate the Uniform Data Set (v3.0) executive function composite scores (UDS3-EF) in patients with mild cognitive impairment (MCI), AD, behavioral variant frontotemporal dementia (bvFTD), and cognitively normal participants.[12] This model was based on several neuropsychological tests including lexical and semantic fluency, backward digit span, and Trails A and B. Additionally, it leveraged item response theory to handle missing data points, preserving its utility in patients unable to complete all of the tests in a battery. One novelty of this model over the other proposed EF composite scores is the use of nonlinear demographic data (i.e., age, sex, and years of education) adjustments, which more accurately captures the complex relationships between cognitive decline and age, among other variables.

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) share many clinical, genetic, and pathological features that have led to the appreciation of the FTD-ALS disease spectrum. FTD is a neurological disorder characterized by behavioral, cognitive, and motor impairment due to neurodegeneration in the frontal and temporal lobes.[13] ALS is defined by progressive motor dysfunction due to degeneration of upper and lower motor neurons. Half of all patients with ALS have varying severity of cognitive and/or behavioral symptoms and approximately 15% meet the diagnostic criteria for FTD.[14,15] Executive dysfunction is a hallmark of this disease spectrum and a potential marker of progression.[16,17] This uniform measure of executive function may help to identify FTD-ALS spectrum patients who lack capacity. In this paper, we examine the relationship between the UDS3-EF composite score and decisional capacity, as well as the relationships between this composite score and other clinical measures in FTD-ALS spectrum patients.

Methods

Cohort

All participants were evaluated in the National Institute of Neurological Disorders and Stroke Neurodegenerative Disorders Clinic. Eligible individuals were enrolled in the National Institutes of Health (NIH) IRB approved protocol "Investigating Complex Neurodegenerative Disorders Related to Amyotrophic Lateral Sclerosis and Frontotemporal Dementia" (clinicaltrials.gov identifier: NCT03225144). Standardized determination of capacity was performed at the time of consent using a six-item questionnaire. Participants underwent a standardized battery of tests, including neurological examination, neuropsychological assessment, and motor evaluation. The clinical history, diagnostic test results, and diagnosis were reviewed at a consensus conference held after the study visit. For participants whose consensus clinical diagnosis was unclear, records were reviewed by board-certified subspecialists (JK, AS) to determine the final diagnosis for this analysis. Internal and external medical records and questionnaires were reviewed, and symptom duration was calculated based on the earliest estimated time of symptom onset as documented in all available data.

One hundred and sixty-two participants were enrolled from the start of the protocol in 2017 through May 2022. One participant withdrew from the study. Participants who did not undergo neuropsychological testing (n = 4), those for whom English was a second language (n = 24), and individuals with fewer than three of the specified tests (n = 11) were excluded from the analysis. Of those individuals excluded from the analysis because of limited neuropsychological testing, 3 of 11 lacked decisional capacity, and of those with no testing, two of four lacked decisional capacity. Patients without qualifying diagnoses (n = 17) were also excluded (Fig. 1). Participants were grouped into "ALS," "FTD," or "Other" categories. The "ALS" cohort included all variants of ALS including primary lateral sclerosis (PLS). The "FTD" cohort consisted of behavioral variant (bvFTD), semantic and non-fluent variants of primary progressive aphasias (PPA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), while the "Other" cohort consisted of presymptomatic *C9orf72* hexanucleotide repeat expansion (HRE) carriers, mild cognitive impairment (MCI), Alzheimer's disease (AD), logopenic PPA (lvPPA), Parkinson's disease (PD), Lewy body dementia (LBD), multiple system atrophy (MSA), hereditary spastic paraparesis (HSP), spinal cerebellar ataxia (SCA), and neurodegenerative disorder

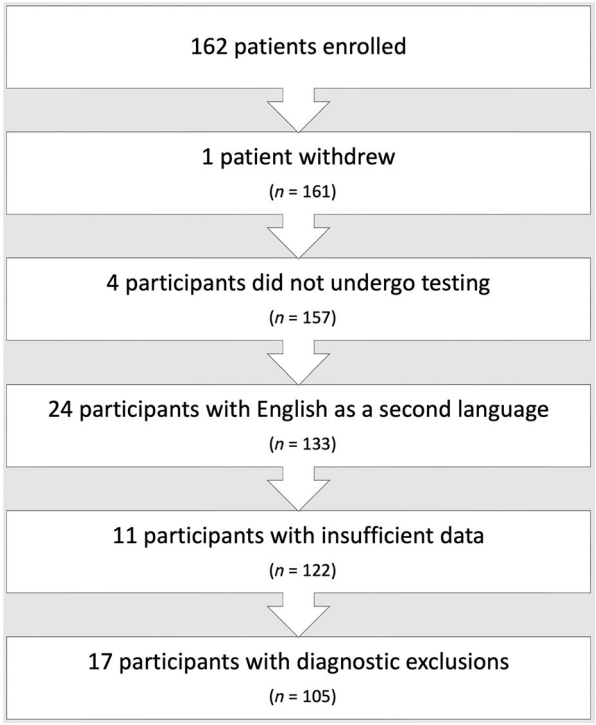

Figure 1. Diagram of participant flow.

not otherwise specified (NOS). Patient demographics and clinical characteristics are summarized in Table 1.

Clinical assessment

The clinical assessments included a standardized capacity determination, neurological history and examination, neuropsychological testing, and informant interview.

A six-item capacity assessment questionnaire referring to the content of the research study was designed to address the four pillars of capacity: communication of a choice, understanding relevant information, appreciation for their situation and the consequences of a choice, and the rational manipulation of information (Fig. S1).[3,18] The questionnaire was verbally administered during the informed consent process. If any item was answered incorrectly, the material was reviewed, and the participant was allowed to answer again. If the response was again incorrect, the participant was deemed not to have capacity, and informed consent was obtained from the surrogate.

The Neuropsychiatric Inventory (NPI) and Clinical Dementia Rating (CDR)© were obtained through patient and informant interviews.[19–23] The CDR© plus NACC FTLD (National Alzheimer Coordinating Center Frontotemporal Lobar Degeneration) standard and supplemental sum of boxes, henceforth referred to as SB, were included in the analysis.[24–26] In participants whose SB scores were not obtained, the scores were determined by consensus from members of the research team based on a review of records and clinical assessments (JK, JF, TH). Because the aim of this study was to examine the effect of cognition on decisional capacity, SB was used as the proxy for disease severity instead of the ALS Functional Rating Scale, Revised in ALS patients.

Executive function composite score

A comprehensive neuropsychological battery was administered as part of the standard research visit. Semantic fluency (number of correct animal words per minute), phonemic fluency (number of correct F words per minute), Trail Making Test (number of correct lines per completion time; if incomplete, a maximum time of 300 seconds was used for Trail Making Test B), and backwards digit span were imputed into the UDS3-EF

Table 1. Summary of demographic data.

	ALS[a]	FTD[b]	Other[c]
N (% female)	39 (54)	40 (45)	26 (50)
Age, years (SD)	58.05 (11.41)	65.53 (7.96)	58.54 (11.54)
Education, years (SD)	16.46 (2.29)	16.08 (2.41)	15.69 (2.32)
Symptom duration, median months (range)[d]	21.80 (2.70 to 118.50)	46.10 (12.80 to 361.30)	46.80 (12.90 to 178.90)
SB, mean (SD)	0.15 (0.35)	5.13 (4.18)	3.23 (5.31)
NPI, median (range)	1 (0 to 19)	10 (0 to 55)	3 (0 to 37)
EF score, mean (SD)	−0.52 (1.25)	−2.86 (1.26)	−1.90 (1.41)
Patients without capacity (%)	0 (0)	10 (25)	5 (19)

[a]ALS includes ALS (35) and PLS (4).
[b]FTD includes bvFTD (10), svPPA and nfvPPA (9), and CBS and PSP (21).
[c]Other includes PD (2), MSA (1), SCA (1), MCI (3), AD (5), lvPPA (1), LBD (1), pre-symptomatic C9orf72 repeat expansion carrier (5), HSP (1), and neurodegenerative disorders NOS (7).
[d]Pre-symptomatic *C9orf72* HRE genetic mutation carriers were excluded from symptom duration calculations.

algorithm.[12] The UDS3-EF tests of "L" word and vegetable fluency were not components of the administered neuropsychological battery and were left blank. Missing values due to participants' inability to complete a task, administration error, or technical errors, were also left blank for the analyses. The NIH cohort was demographically similar to the originally published validation cohort, and therefore the demographic-adjusted model was used (Table S1). Lower EF scores indicated greater impairment. The UDS3-EF R script was run on R 4.2.0.[27]

Statistical analysis

Descriptive statistics were reported for each of the following quantitative or categorical variables: participant demographics, clinical characteristics, and EF scores. The EF score was considered the primary explanatory variable with all other variables being secondary. Decisional capacity (with versus without) was the dependent variable. Simple logistic regression was performed to examine the effect of each variable on decisional capacity. Firth's penalized likelihood approach was applied to calculate the odds ratio and 95% confidence intervals. Spearman correlation coefficients were used to evaluate the linear relationship between the five quantitative variables (age, education, symptom duration, NPI, and SB) and the EF score. Two-sample *t*-test/Wilcoxon rank-sum test and Fisher's exact test were applied to assess the patient group effect on quantitative and categorical variables respectively. A significance level of $\alpha = 0.05$ was used. All the statistical analyses were performed using SAS version 9.4.

Results

Demographics

One hundred and five participants were included in the analyses and consisted of 39 ALS, 40 FTD, and 26 in the Other group. There were 52 women and 53 men. The mean age of symptom onset was 58.05 (SD = 11.41) years in ALS, 65.53 (SD = 7.96) years in FTD, and 58.54 (SD = 11.54) years in Other. The median symptom duration was 21.80 (range 2.70 to 118.50) months in ALS, 46.10 (range 12.80 to 361.30) months in FTD, and 46.80 (range 12.90 to 178.90) months in Other. The mean years of education were similar in all groups. The median NPI score was 1 (range 0 to 19) in ALS, 10 (range 0 to 55) in FTD, and 3 (range 0 to 37) in Other. The mean SB scores were 0.15 (SD = 0.35) in ALS, 5.13 (SD = 4.18) in FTD, and 3.23 (SD = 5.31) in Other. The demographic and clinical characteristics of the participants at the time of enrollment are summarized in Table 1.

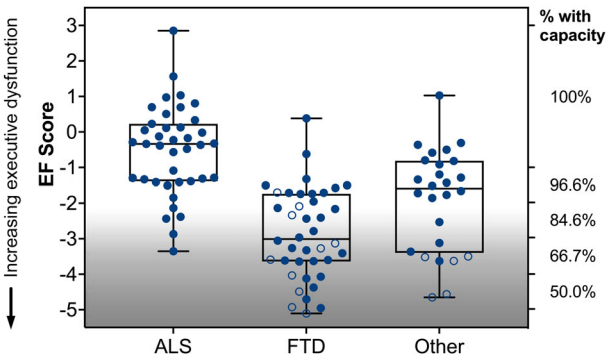

Figure 2. Executive function (EF) scores (left) and decision capacity by diagnostic categories. Close circle = preserved decisional capacity. Open circle = lacked decisional capacity.

Executive function

Most participants in this cohort had impaired executive function with a mean EF score of −1.75 (SD = 1.65) with a range from −5.10 to 2.85, where more negative scores indicate greater impairment (Fig. 2). The EF scores differed significantly between groups (Tables 1 and 2) and were the highest in ALS (−0.52, SD = 1.25) followed by the Other group (−1.90, SD = 1.41). Executive function was most impaired in FTD with the lowest mean EF score (−2.86, SD = 1.26) (Fig. 2). There was a strong association between executive function and overall disease severity; the EF score strongly correlated with the SB ($r = -0.667$) (Figs. 3A and S2). The EF score also showed a moderate correlation to the NPI (Figs. 3B and S2), indicating a relationship between executive function and behavioral impairment ($r = -0.436$). Executive function was not strongly associated with symptom duration, education, or age ($r = -0.230$, $r = 0.074$, $r = -0.299$, respectively) (Fig. S2).

Capacity

In total, 15 participants lacked capacity. Executive function was a strong predictor of capacity to provide informed consent. Each point decrease in EF score, corresponding to more executive dysfunction, increased the

Table 2. Tukey post-hoc analysis of executive function scores between diagnosis groups.

Comparison groups	Difference	95% CI	*p*
ALS vs. FTD	−2.34	−3.04 to −1.63	**0.001**
ALS vs. Other	−1.38	−2.17 to −0.59	**0.001**
FTD vs. Other	0.95	0.17 to 1.74	**0.013**

$p < 0.05$ in bold.

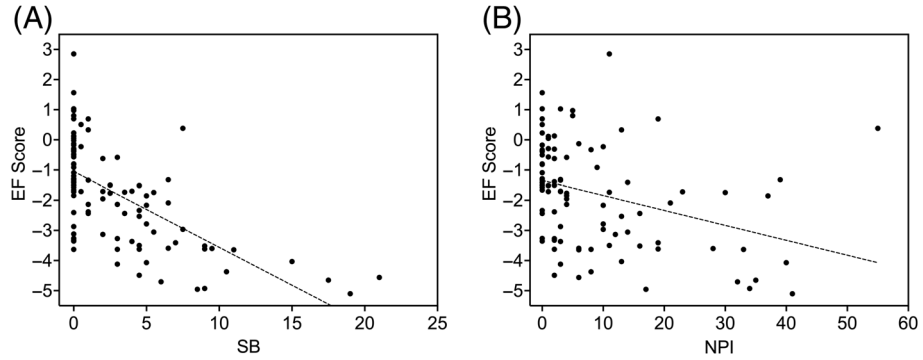

Figure 3. (A) Executive function score versus the CDR© plus NACC FTLD standard and supplemental sum of boxes (SB), $r = -0.667$, $p < 0.0001$. (B) Executive function (EF) score versus neuropsychiatric index (NPI), $r = -0.436$, $p < 0.001$.

Table 3. Odds of impaired decisional capacity.

Parameter	Odds ratio	95% CI	*p*
Gender (female vs. male)	0.66	0.22 to 1.95	0.4461
Diagnosis groups			
FTD vs. ALS	25.82	1.40 to 476.76	**0.0288**
Other vs. ALS	17.56	0.89 to 346.19	0.0596
FTD vs. other	1.47	0.45 to 4.80	0.5222
EF score	2.92	1.66 to 5.13	**0.0002**
SB	1.38	1.17 to 1.63	**<0.0001**
NPI (log-scale)	1.66	1.05 to 2.75	**0.037**
Symptom duration (log month-scale)	2.14	1.07 to 4.25	**0.0307**
Education level (years)	0.86	0.69 to 1.08	0.2036
Age (years)	1.05	0.99 to 1.11	0.0908
Head injury (yes vs. no)	2.25	0.71 to 7.12	0.1681

$p < 0.05$ in bold.

likelihood of impaired decisional capacity by nearly two-fold (OR = 2.92, 95% CI [1.66–5.13], $p = 0.0002$). A higher SB, corresponding to greater disease severity, also increased the likelihood of a participant lacking decisional capacity (OR = 1.38, 95% CI [1.17–1.63], $p < 0.0001$) (Table 3). Compared to no impairment, any impairment as measured by SB showed an increased risk of lacking capacity (OR = 32.54, 95% CI [1.95–543.18], $p = 0.0153$) (Table S2). Dementia rating scale subdomain analysis showed that each component score was significantly associated with capacity, except for personal care (Table S2). For each point increase in NPI, the likelihood of lacking decisional capacity increased by 66% (OR = 1.66, 95% CI [1.05–2.75], $p = 0.037$).

The ability to provide decisional capacity differed by diagnosis (Tables 1 and 3 and Fig. 2). All ALS participants had capacity, whereas 25% ($n = 10$) of FTD participants and 18% ($n = 5$) of Other participants lacked capacity ($p = 0.0017$). Compared to ALS patients, FTD patients were 25 times more likely to lack capacity (OR = 25.82, 95% CI [1.40–476.76], $p = 0.0288$). There was no significant difference in the likelihood of having decisional capacity when comparing ALS versus Others (OR = 17.56, 95% CI [0.89–346.19], $p = 0.0596$) and FTD versus Others (OR = 1.47, 95% CI [0.45–4.80], $p = 0.5222$).

In this cohort, it is interesting that symptom duration was not strongly associated with SB, a measure of disease severity ($r = 0.263$) (Fig. S2). However, longer symptom duration increased the likelihood of impaired decision capacity by 110% (OR = 2.14, 95% CI [1.07–4.25], $p = 0.0307$) whereas gender, education level, and age did not (OR = 0.66, $p = 0.4461$; OR = 0.86, $p = 0.2036$; OR = 1.05, $p = 0.0908$, respectively) (Table 3). Additionally, a history of head injury was not predictive of decisional capacity (OR = 2.25, $p = 0.1681$) (Table 3).

Discussion

This is the first study to systematically examine the relationship between decisional capacity in research and cognitive performance across neurodegenerative disorders. Using the newly developed UDS3-EF score, an executive function composite score, we showed a two-fold increase in impaired capacity to provide informed consent for each incremental decrease in executive function. ALS participants demonstrated modest executive dysfunction on UDS3-EF, and none lacked capacity. In contrast, the FTD participants showed severe executive dysfunction and were two-fold more likely to lack capacity.

The Declaration of Helsinki specifically identifies individuals who are vulnerable and unable to consent for themselves as requiring additional protection in research.[28] In 2009, the United States Department of Health and Human Services Office for Human Research

Protection mandated greater oversight in research studies that included patients diagnosed with neurodegenerative disorders because of the unique risk of this population to coercion and exploitation.[29] These patients are at high risk for cognitive impairment, and yet capacity status cannot be assumed based on the diagnosis.[30] Careful consideration is required in neurodegenerative research during the process of determining the capacity to consent.

Neurodegenerative disorders can affect different cognitive domains to varying degrees of severity. Executive function is the higher-order process that dictates goal-driven behavior, which contributes to decisional capacity, including electing to participate in research.[31] Previous works have shown an association between impaired capacity and specific elements of executive function, such as short-term memory, attention, and verbal fluency.[32–34] Typically, single measures of executive function do not capture the full scope of this cognitive domain. Moreover, the inclusion of additional tests to bedside cognitive screens have added value when determining capacity.[35] This highlights the importance of having a global assessment of executive function prior to assessing capacity for research. The UDS3-EF score is a comprehensive assessment of all the subdomains of executive function.[12]

Unsurprisingly, while most participants in this study have some degree of executive dysfunction, this was mild in ALS and most severe in FTD. Correspondingly, decisional capacity was preserved in ALS, while lack of capacity paralleled increasing executive dysfunction in the remaining cohort. Most patients who lacked capacity had an executive function composite score lower than −3. While the SB strongly correlates to the executive function composite score, the former is a measure of function while the latter is of cognition. Of those individuals with UDS3-EFS lower than −3, most had impaired function as measured by the disease severity (Fig. 3A). Although executive function and disease severity measures are two important elements that contribute to capacity assessment, none are deterministic. Capacity to consent to research is complex and requires careful consideration of a multitude of factors, including the nature of risks associated with the research itself.

When considering the practical implications of this work, several findings are of note. Data regarding disease severity and executive function status from the clinical evaluation are most important for identifying individuals at risk for lack of capacity to consent to research. In our study, SB was correlated with UDS-EF3 and UDS-EF3 predicted capacity status; therefore, disease severity is an important index for participants at risk. Moreover, our study suggests that a UDS-EF3 score of less than −3 may be a cutoff below which individuals are likely to lack capacity. Education and age were not correlated with capacity status and therefore neither should serve as clinical metrics for flagging at-risk individuals. Additionally, a neurodegenerative diagnosis alone does not inevitably result in lacking capacity to consent to research. ALS patients without cognitive impairment have preserved capacity whereas patients with disorders impacting cognition are at higher risk. Neurodegenerative disorders as a group do not carry equal risk—it is the involvement of cognition that enhances the risk of decisional impairment.

Our study has a few limitations. While the cohort spans the FTD-ALS phenotypic spectrum, the number of participants is relatively small. Moreover, cognitive and behavioral impairment in ALS participants tends to be mild and no ALS participants met criteria for FTD. Thus, our sample might not adequately represent those individuals with combined ALS and FTD. An additional limitation is the six-item questionnaire used for capacity assessment. While it incorporated the tenets of informed consent and was applied systematically in all participants, it has not been externally validated. Another unique feature in this cohort is that those who participate in research at the NIH tend to be knowledgeable of research and more motivated and engaged, which may not be reflective of participants elsewhere.

In our cohort, five individuals in the Other category were pre-symptomatic *C9orf72* HRE mutation carriers. None of these individuals lacked decisional capacity to provide research informed consent. However, all of these individuals showed mild executive dysfunction, consistent with the literature describing subtle abnormalities in this group prior to frank phenoconversion.[36,37] Given the pattern of cognitive changes in carriers of the *C9orf72* mutation, this group may warrant increased scrutiny and could be explored in future analyses.

Another limitation of our study is the exclusion of severely impaired patients. In our study, 15 individuals were excluded from the analysis because of inability to complete some or all neuropsychological tests resulting in insufficient or absent neuropsychological data. Five of these patients were found to lack the decisional capacity for research consent. Of these, none were diagnosed with ALS and all had advanced disease with profound cognitive and/or behavioral impairment. Excluding these participants results is underestimating the odds of lacking decisional capacity in the setting of executive dysfunction.

In this study, we demonstrate the relationship between decisional capacity and cognitive impairment in a neurodegenerative cohort and find that executive dysfunction increases the odds of lacking decisional capacity and is strongly correlated with disease severity. The hallmark of these disorders is executive dysfunction, and this patient population is prespecified as being vulnerable and

requiring protection. The need to assess decisional capacity, while recognized, remains a major gap in the informed consent process and a critical area for improvement in neurodegenerative research.

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Author Contributions

Study conception and design: Makayla Portley, Carolyn Sherer, Tianxia Wu, Jennifer Farren, Allison Snyder, Justin Y. Kwan. *Data collection*: Jennifer Farren, Sonja W. Scholz, Bryan J. Traynor, Michael E. Ward, Taryn Haselhuhn, Allison Snyder, Justin Y. Kwan. *Analysis and interpretation of results*: Makayla Portley, Carolyn Sherer, Tianxia Wu, Laura E. Danielian, Allison Snyder, Justin Y. Kwan. *Draft manuscript preparation*: Makayla Portley, Tianxia Wu, Laura E. Danielian, Allison Snyder, Justin Y. Kwan. All authors reviewed the results and approved the final version of the manuscript.

Disclosures

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Figure 1 Capacity assessment questionnaire adapted from Jeste et al.[18]

Supplementary Figure 2 Spearman correlation coefficients between quantitative variables. NPI = Neuropsychiatric inventory, SB = The CDR© plus NACC FTLD (National Alzheimer Coordinating Center Frontotemporal Lobar Degeneration) standard and supplemental sum of boxes, EF = Executive function.

Supplementary Table 1